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Executive summary of the American Radium Society appropriate use criteria for management of uterine clear cell and serous carcinomas

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ABSTRACT

Background Uterine clear cell and serous carcinomas have a high propensity for locoregional and distant spread, tend to be more advanced at presentation, and carry a higher risk of recurrence and death than endometrioid cancers. Limited prospective data exist to guide evidence-based management of these rare malignancies.

Objective The American Radium Society sought to summarize evidence-based guidelines developed by a multidisciplinary expert panel that help to guide the management of uterine clear cell and serous carcinomas.

Methods The American Radium Society Appropriate Use Criteria presented in this manuscript were developed by a multidisciplinary expert panel using an extensive analysis of current published literature from peer-reviewed journals. A well-established methodology (modified Delphi) was used to rate the appropriate use of diagnostic and therapeutic procedures for the management of uterine clear cell and serous carcinomas.

Results The primary treatment for non-metastatic uterine clear cell and serous carcinomas is complete surgical staging, with total hysterectomy, salpingo-oophorectomy, omentectomy, and lymph node staging. Even in early-stage disease, patients with uterine clear cell and serous carcinomas have a worse prognosis than those with type I endometrial cancers, warranting consideration for adjuvant therapy regardless of the stage. Given the aggressive nature of these malignancies, and until further research determines the most appropriate adjuvant therapy, it may be reasonable to counsel patients about combined-modality treatment with systemic chemotherapy and radiotherapy.

Conclusion Patients diagnosed with uterine clear cell and serous carcinomas should undergo complete surgical staging. Multimodal adjuvant therapies should be considered in the treatment of both early-stage and advanced-stage disease. Further prospective studies or multi-institutional retrospective studies are warranted to determine optimal sequencing of therapy and appropriate management of patients based on their unique risk factors. Long-term surveillance is indicated due to the high risk of locoregional and distant recurrence.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Uterine clear cell and serous carcinomas have been under-represented in large prospective trials. The optimal treatment paradigm for each histology remains somewhat undefined.

WHAT THIS STUDY ADDS

⇒ We review current evidence supporting the staging work-up, and surgical and adjuvant management of early-stage and advanced-stage uterine clear cell and serous carcinomas

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The discussion of evidence and appropriateness rating presented here can serve as a guide to practitioners in the diagnostic and therapeutic management of uterine clear cell and serous carcinomas.

INTRODUCTION

Endometrial cancer is the most common gynecological cancer in the USA and the sixth most common cause of cancer in women worldwide.[1] Uterine clear cell and serous carcinomas represent an aggressive subset of endometrial cancers which tend to be more advanced at presentation and carry a higher risk of death than type I endometrioid cancers.[2] Even in early-stage disease, patients with uterine clear cell and serous carcinomas have a worse prognosis than those with type I endometrial cancers, prompting consideration for adjuvant therapy regardless of the stage. However, no clear consensus has been established.

Both uterine clear cell and serous carcinomas have historically been pooled into studies with other high-risk uterine cancers, rather than studied exclusively in prospective clinical trials. Thus, the optimal treatment paradigm for each histology remains undefined, especially in early-stage disease. For the purposes of this review, early-stage disease is that confined to the uterus/cervix (stage I/II), and late/advanced-stage

disease is any extra-uterine or cervical spread (stage III/IV). Adjuvant therapy options include chemotherapy, vaginal cuff brachytherapy and pelvic±para-aortic external beam radiotherapy, or both, with multimodality therapy typically considered for these aggressive tumors.

METHODS

The expert panel on Radiation Oncology–Gynecology is composed of 15 members with the multidisciplinary expertise required to competently complete the Appropriate Use Criteria projects. The chair is appointed by the president-elect of the American Radium Society. Panelists are appointed for a term of 3–5 years. Panel members responsible for this project and complete details about the Appropriate Use Criteria committee membership procedures are listed in the online supplemental materials 1.

An extensive and updated analysis of current medical literature from peer-reviewed journals from January 1, 1996 to January 28, 2020 was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses[3] guidelines to search the PubMed, Embase, and Web of Science databases to retrieve a comprehensive set of relevant articles. We developed strategies using subject and combinations of search terms. We reviewed the bibliographies of full articles for a comprehensive survey, and relevant studies were included. The literature was reviewed for quality of study design, cohort size, selection bias, variability of evaluation of participants in regard to time from exposure, and methods of assessments. In addition, two studies published after the literature review were added during the writing of the manuscript given their significant relevance to the topic.

A well-established consensus methodology (modified Delphi)[4] was used to rate the appropriateness of treatment procedures by the expert panel. The expert panel was composed of a multidisciplinary panel of radiation and gynecologic oncologists as well as a radiologist with expertise in the management of uterine cancer.

RESULTS

Rationale for Comprehensive Surgical Staging

Primary treatment for non-metastatic uterine clear cell and serous carcinomas is complete surgical staging with total hysterectomy, bilateral salpingo-oophorectomy, lymph node staging, omentectomy, and sampling peritoneal washings for cytology. The preferred surgical approach has not been thoroughly investigated; while the LAP2 trial demonstrated feasibility and safety of a laparoscopic approach for endometrial cancers, only 12% of patients in that study had uterine clear cell and serous carcinomas.[5] In a post hoc analysis of patients with uterine clear cell and serous carcinomas, patterns of recurrence and survival were not affected by the surgical approach.[6] In general, when technically feasible, a minimally invasive surgical approach is preferred. Given the propensity for extra-uterine spread, pre-operative CA-125 and CT chest/abdomen/pelvis and/or MRI to evaluate for metastatic disease are recommended by the Society of Gynecological Oncology.[7] The role of PET/CT is unclear as it can be difficult to distinguish 18-fluorodeoxyglucose uptake in bowel from peritoneal implants.

Often, patients present with metastatic disease, which has led to the consideration of neoadjuvant chemotherapy prior to cytoreductive surgery. Recent data from a National Cancer Database review suggests use of this approach accounts for nearly one-quarter of patients who present with stage IV disease.[8] Relative to propensity-score-matched patients undergoing upfront surgery, those undergoing neoadjuvant chemotherapy had decreased mortality during the early months following diagnosis. This benefit, however, was lost after approximately 8 months and patients with longer survival had better outcomes with primary surgery. Given the current expansion in risk stratification and individualized treatment options, more investigation is needed to understand the optimal surgical approach for patients with de novo stage IV disease.

Rationale for Adjuvant Radiotherapy Alone

The Gynecologic Oncology Group (GOG) conducted a phase II study, GOG 94, evaluating the role of whole abdominal radiotherapy in stage I/II uterine clear cell and serous carcinomas.[9] Following debulking to <2 cm residual disease (omentectomy not required), 34 patients received whole abdominal radiotherapy to 30 Gy at 1.5 Gy per fraction, with a pelvic boost of 19.8 Gy at 1.8 Gy per fraction. Patients with uterine clear cell carcinoma (13 patients) had a higher 5-year progression-free survival than those with uterine serous carcinoma (21 patients), 54% vs 38%, respectively. Still, over half of all recurrences were in the radiotherapy field, suggesting that whole abdominal radiotherapy alone was not adequate.[9] In addition, there was a 17% rate of grade 3–4 gastrointestinal toxicity, much higher than is observed in modern series using conformal techniques. While this study used outdated radiation techniques, the results suggest that uterine clear cell carcinomas might have better outcomes than uterine serous carcinomas. The results also raised concern that chemotherapy should be considered in combination with radiotherapy for patients with both histologies.

In the pooled analysis of high-risk endometrial cancers treated on the randomized NSGO-EC-9501/EORTC-55991 and MaNGO-ILIADE-III trials, where radiotherapy alone was compared with radiotherapy combined with chemotherapy, the addition of chemotherapy to radiotherapy resulted in an overall 36% reduction in risk of relapse or death when all histologies were combined. However, among the 140 patients with uterine clear cell and serous carcinomas, the benefit of chemotherapy was not demonstrated.[10] Comparably, a National Cancer Database review of uterine serous carcinomas suggested a survival benefit from vaginal brachytherapy in stage IA/II disease, while only stage IB/II disease demonstrated a survival benefit from chemotherapy.[11] A second National Cancer Database review also observed a survival benefit from adjuvant vaginal brachytherapy for both invasive and non-invasive stage IA uterine clear cell and serous carcinomas.[12] For non-myoinvasive stage IA tumors, the benefit of adjuvant therapy is less clear and may be limited to those patients who have not undergone a staging lymphadenectomy.[13]

Lastly, the phase III GOG 0249 trial included a subset of patients with stage I/II uterine clear cell and serous carcinomas (88 with uterine serous and 28 with uterine clear cell carcinomas). Patients were randomized to pelvic radiotherapy (45–50.4 Gy), or vaginal brachytherapy plus three cycles of paclitaxel and carboplatin. At 53 months' median follow-up, combined vaginal

brachytherapy-chemotherapy was not superior to pelvic radiotherapy and was associated with more frequent and severe acute toxicity.[14]

Rationale for Adjuvant Chemotherapy Alone

Since the publication of GOG 122, which included 17 patients with uterine clear cell carcinomas and 83 with uterine serous carcinomas, and showed that chemotherapy resulted in improved overall survival compared with whole abdominal radiotherapy (52% vs 42%) in treating locally advanced disease of all histologic subtypes, chemotherapy has become part of the standard treatment for locally advanced disease.[15] However, chemotherapy was also associated with increased grade 3–4 toxicities and resulted in nearly 20% risk of locoregional recurrence. Moreover, the overall poor survival outcomes with each mono-modal approach highlight the need for improved treatment strategies. While the radiotherapy techniques used in this study are outdated, the observed improved survival nevertheless provided support for chemotherapy as standard treatment for locally advanced endometrial cancers of all histologic subtypes.

A more recent prospective study, GOG 0258, included a subset of patients with stage I–II uterine clear cell and serous carcinomas with positive peritoneal cytology; 131 patients with uterine serous carcinomas and 22 with uterine clear cell carcinomas. Patients were randomized between chemoradiotherapy and chemotherapy alone (carboplatin plus paclitaxel) for six cycles. The combined chemoradiotherapy arm consisted of pelvic radiotherapy to 45 Gy with concurrent cisplatin followed by four cycles of carboplatin and paclitaxel. At 60 months, chemoradiotherapy was associated with a lower incidence of vaginal recurrence (2% vs 7%; HR=0.36) and pelvic and para-aortic lymph node recurrence (11% vs 20%; HR=0.43) than chemotherapy alone. Nevertheless, distant recurrence appeared more common in the chemoradiotherapy arm (27% vs 21%; HR=1.36), and there was no difference in disease-free survival or grade 3–5 toxicity between the two study groups.[16]

Rationale for Combined-Modality Therapy (Chemotherapy and Radiation Treatment)

In light of the high risk of relapse with single-modality therapy for both uterine clear cell and serous carcinomas, a combined-modality approach is often considered in an effort to prevent both local and distant recurrences. For early-stage disease, several retrospective series have evaluated the role of vaginal brachytherapy in combination with chemotherapy. In one multi-institutional analysis of 414 patients with stage IA uterine clear cell and serous carcinomas, vaginal brachytherapy and chemotherapy were both associated with improved local control and disease-free survival on multivariable analysis.[17]

For advanced-stage disease, the value of radiotherapy added to chemotherapy for uterine clear cell and serous carcinomas remains controversial. A prospective phase II study of patients with stage I–IIIA uterine serous carcinomas who underwent adjuvant concurrent weekly paclitaxel (50 mg/m^2) and pelvic radiotherapy to 45 Gy plus vaginal brachytherapy followed by four cycles of adjuvant paclitaxel (135 mg/m^2) resulted in a 5-year overall survival, progression-free survival, and local control rate for all patients of 85%, 83%, and 87%, respectively.[18] This study lends support to consideration of adjuvant concurrent paclitaxel and pelvic radiotherapy followed by four courses of systemic paclitaxel for surgically staged I–III uterine serous carcinomas.

The recently published PORTEC-3 trial investigated the benefit of combined-modality therapy compared with pelvic radiotherapy alone in patients with high-risk endometrial cancer, 105 of whom had uterine serous carcinoma and 62 had uterine clear cell carcinoma, stage I–III. Patients were randomized to pelvic radiotherapy alone (48.6 Gy) or radiotherapy with concurrent cisplatin (two cycles) and adjuvant carboplatin/paclitaxel (four cycles).[19] In the updated analysis, both overall and failure-free survival were significantly improved in patients who received combined-modality therapy, with the greatest benefit in patients with stage III or uterine serous carcinoma, or both. Patients with uterine serous carcinoma were found to have a lower failure-free survival and overall survival than those with other histologies, and for these patients there was a significant improvement in overall survival (absolute improvement 19%) and failure-free survival (absolute improvement 12%) with chemoradiotherapy compared with radiotherapy alone.[20]

While the optimal scheduling of chemotherapy and radiotherapy is not established, a phase II study investigated outcomes associated with pelvic radiotherapy 'sandwiched' between six cycles of carboplatin/paclitaxel in uterine serous carcinoma (three cycles prior to radiotherapy and three cycles following radiotherapy).[21] For stage I/II disease, the 2- and 5 year overall survival was 96% and 81%, respectively. For stage III/IV disease, the 2- and 5 year overall survival was 64% and 18%, respectively.[22] A separate prospective phase II study examined stage I–IVA uterine serous carcinoma treated with sequential adjuvant paclitaxel (175 mg/m^2) and carboplatin (area under curve 6) for four cycles, followed by pelvic radiotherapy (50.4 Gy). Thirteen of 29 patients with stage I–III disease (44.8%) had a recurrence at 28 months, suggesting that further study is needed to determine the optimal sequencing strategy.[23]

Rationale for Targeting Human Epidermal Growth Factor Receptor 2 (HER2)

Overexpression/amplification of the oncogene human epidermal growth factor receptor 2 (HER2) has been identified in uterine clear cell and serous carcinomas to varying degrees,[24–26] and clinical trials are now incorporating anti-HER2 directed therapy into experimental paradigms. A phase II trial evaluated 61 patients with advanced/recurrent uterine serous carcinomas overexpressing HER2 and randomized patients to carboplatin/paclitaxel±trastuzumab. Patients who received trastuzumab had equal toxicity with an improved progression-free survival of 12.6 vs 8.0 months (p=0.005). On subcohort analysis, the greater benefit was seen in patients treated upfront with trastuzumab, compared with those with recurrent disease. In the setting of HER2-expressing locally advanced or recurrent uterine serous carcinoma, emerging data appear to support the consideration of adding trastuzumab to platinum and taxane-based chemotherapy.[27]

Patient-focused Planning Techniques

For patients treated with vaginal brachytherapy, the target volume should include the proximal 3–4 cm of the vaginal canal. Various dose prescriptions could be used, and we endorse those specified by the American Brachytherapy Society guidelines.[28] In addition, given the low morbidity and excellent local control reported with shorter fractionation schemes, a 3, 4, or 5 fraction approach are

preferred compared with longer fractionation regimens. When treating with external beam radiotherapy, a CT-based 3D conformal or intensity-modulated radiotherapy technique should be used. The randomized phase III trial GOG 1203 comparing intensity-modulated radiotherapy with a four-field approach found an improvement in patient-reported gastrointestinal and genitourinary symptoms with intensity-modulated radiotherapy.[29] Similarly, there is probably little to no role for whole abdominal radiotherapy for patients with uterine clear cell and serous carcinomas, as this approach carries a known increased risk in treatment-related toxicity without a known clinical benefit.

When using intensity-modulated radiotherapy, careful delineation of the nodal and vaginal clinical target volumes is necessary. Creating a vaginal internal target volume is recommended to account for inter-fraction motion due to bladder filling and rectal distention. The panel endorses the NRG Oncology international collaborative atlas of contouring guidelines in the post-operative setting.[30] The recommended clinical target volume dose is 45–50.4 Gy at 1.8–2.0 Gy per fraction, and an appropriate planning tumor volume margin is typically 5–7 mm, depending on the immobilization technique and image guidance available.[30]

Surveillance

The panel supports a complete history and abdominopelvic-rectal examination conducted every 3 months for the first 2 years and semiannually thereafter as suggested by the Society of Gynecological Oncology.[31] It is recommended that all symptomatic patients undergo a targeted investigation to rule out recurrence, which often includes CT chest/abdomen/pelvis, MRI and/or PET/CT, depending on the clinical scenario.

Consensus and Recommendations from Expert Panel

- The panel strongly recommends vaginal brachytherapy alone or systemic therapy+vaginal radiotherapy as adjuvant treatment for a non-invasive surgically staged International Federation of Gynecology and Obstetrics (FIGO) stage IA uterine clear cell and serous carcinomas.
- For patients who had a hysterectomy without lymph node dissection, a pelvic and para-aortic lymph node dissection may be appropriate, depending on the patient's unique risk factors and goals of therapy.
- Adjuvant chemotherapy and radiation therapy is usually appropriate for a typical case of FIGO stage IB uterine clear cell and serous carcinomas; an exception is the option for pelvic radiotherapy alone for a surgically staged IB uterine clear cell carcinoma with minimal risk features.
- Carboplatin and paclitaxel is usually appropriate for patients treated with adjuvant chemotherapy. Consideration may be made for concurrent cisplatin during external beam radiotherapy, but there was disagreement among the panel about the appropriate schedule (weekly vs every 3 weeks) for concurrent cisplatin.

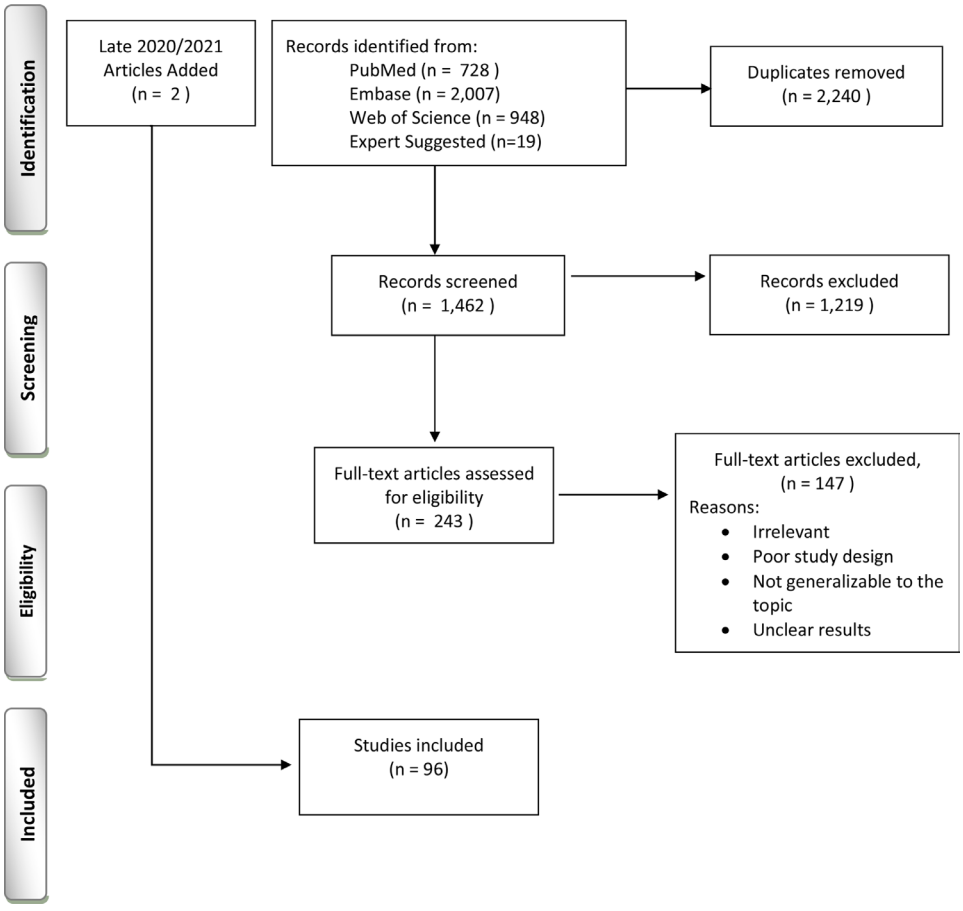

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram: searches run on January 28, 2020.

- Tumor volume-directed radiation treatment is usually appropriate in the adjuvant setting of patients with advanced-stage uterine clear cell and serous carcinomas. There are insufficient data to support the routine use of one radiation technique over the other (vaginal brachytherapy vs external beam radiotherapy) when used in combination with chemotherapy. Intensity-modulated radiotherapy is the recommended technique when external beam radiotherapy is recommended. For patients who undergo pelvic and para-aortic lymph node dissection and are pN0, the panel recommends omitting the para-aortic nodes from the external beam field. There was disagreement on whether to target para-aortic lymph nodes when the pelvic lymph nodes are known to be involved yet the para-aortic sampling was negative.
- For patients receiving vaginal brachytherapy, targeting the entire vaginal length was not recommended by panel members. In addition, the panel endorses the American Brachytherapy Society guidelines, preferring 3, 4, or 5 fraction regimens compared with longer fractionation regimens.
- Routine use of adjuvant whole abdominal radiotherapy is not recommended outside of a clinical trial setting.
- For patients with residual nodal disease after surgery, the panel recommends treatment with definitive intent when feasible. When boosting gross residual nodal disease, the panel thought a simultaneous integrated boost and sequential boost were both reasonable options.
- In the setting of locally advanced uterine serous carcinoma, the panel recommends ordering HER2 testing and consideration for HER2-directed therapy if a tumor is known to be HER2-positive.
- Routine surveillance after treatment with routine imaging in the first 3 years is recommended. There was disagreement among the panel about whether this should be done every 3, 6, or 12 months.

The American Radium Society Appropriate Use Criteria and its expert panels have developed criteria for determining appropriate radiologic procedures for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions about radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the US Food and Drug Administration have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision about the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

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